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Cyclopropanation of Unsaturated Compounds with Diazomethane Generated *in situ*: A New Efficient and Practical Route to Cyclopropane Derivatives

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The synthesis of the title compounds is easily achieved by the Pd-catalysed cyclopropanation of unsaturated compounds with diazomethane generated *in situ* from *N*-methyl-*N*-nitrosourea–KOH in CH_2Cl_2–Et_2O.

Catalytic interaction of diazomethane with unsaturated compounds is a well known synthetic method[1] for the preparation of a wide variety of cyclopropane derivatives. Use of palladium-based catalysts has proved especially successful.[2] The cyclopropanation of strained cyclic and monosubstituted alkenes proceeds with high selectivity, affording cyclopropanes in high yields. However, the standard procedure for cyclopropanation has some important shortcomings. The main limitation is the necessity of preliminary preparation and transportation of toxic and explosive diazomethane.

This communication describes a new safe and efficient procedure for catalytic cyclopropanation of unsaturated compounds with diazomethane. The above mentioned problem with diazomethane is successfully overcome by experimental combination of two key stages of the process: the generation of diazomethane and catalytic cyclopropanation of alkenes with the latter.

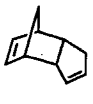
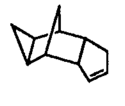
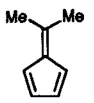
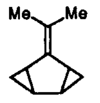
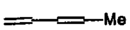
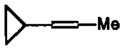
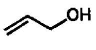
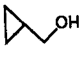
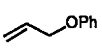
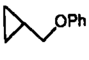
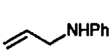
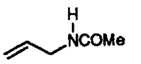
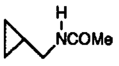
The general pathway is shown in Scheme 1. In order to generate the diazomethane we used *N*-methyl-*N*-nitrosourea which is still one of the most favoured reagents for preparation of diazomethane.[3] The parent alkenes are listed in Table 1 and contain vinyl and strained cyclic double bonds for which the standard Pd-catalysed cyclopropanation procedure works well. In accordance with our earlier results[2] for this process we chose Pd-compounds which easily form low-valent palladium π-alkenic complexes with the parent alkenes, these complexes act as catalysts. Thus, one would expect the one-pot palladium-catalysed cyclopropanation, under the conditions required for alkaline cleavage of *N*-methyl-*N*-nitrosourea, to proceed without hydrolysis and deactivation of the catalytic system.

Our first attempts to realize the cyclopropanation *in situ* were carried out using previously prepared Pd^0 complexes. Addition of *N*-methyl-*N*-nitrosourea to a stirred mixture of norbornene, 0.06–0.1 mol% $[(PhO)_3P]_4Pd$ in CH_2Cl_2 and a solution of KOH at 10–20 °C led to nitrogen evolution and formation of tricyclo[3.2.1.0^{2,4}]octane (95% yield if the *N*-methyl-*N*-nitrosourea/substrate ratio is 1.5:1).

Further investigations showed that more readily available Pd-compounds such as $(PhCN)_2PdCl_2$, $[(PhO)_3P]_2\cdot PdCl_2$, $Pd(acac)_2$, (Hacac = pentane-2,4-dione) and $Pd(OAc)_2$ may also be successfully used. The solutions of the catalysts in CH_2Cl_2 are added with the first portions of *N*-methyl-*N*-nitrosourea. It is important to note that the activity of the catalytic system is not reduced and it allows us to carry out cyclopropanation with yields analogous to *ex situ* procedures.[4] The addition rate of *N*-methyl-*N*-nitrosourea is 50–80 g h^{-1} per 0.1 g Pd, contained

Scheme 1

Table 1 Catalytic cyclopropanation of unsaturated compounds with diazomethane generated *in situ* from *N*-methyl-*N*-nitrosourea (NMU)–KOH [catalyst: 0.1 mol% $(PhCN)_2PdCl_2$, temp. 12–15 °C]

Unsaturated compound	NMU:UC mol. ratio	Solvent	Product[a]		B.p./°C (mbar)	Yield(%)
	1.5:1	CH_2Cl_2		**1**	134–135	95
	2.9:1	CH_2Cl_2		**2**	61–62 (20)	92
	1.5:1	CH_2Cl_2–hexane	 [b]	**3**	92–93 (12)	94
	3:1	CH_2Cl_2–Et_2O	 [c]	**4**	95–97 (80)	84
	1.6:1	CH_2Cl_2		**5**	71–72	92
	1.9:1	Et_2O		**6**	122–123	92
	1.7:1	CH_2Cl_2		**7**	93–95 (17)	91
	1.8:1	CH_2Cl_2–Et_2O		**8**	68–70 (3)	88
	1.9:1	CH_2Cl_2–Et_2O	 [d]	**9**	71–72 (0.3)	73

[a] All compounds were characterized by 250 MHz ^1H NMR spectroscopy and mass spectrometry and have been prepared previously. ^1H NMR spectra were not obtained for cyclopropane compounds **3**, **4** and **9**. [b] ^1H NMR data: $\delta(CDCl_3)$ 5.69, 5.56 m (CH═CH), 3.08 m (1H), 2.1–2.6 (5H), 1.07 dt ($1H^{11}$, ^2J 10.5, J 2 Hz), 0.83 m (2H), 0.51 m (1H), 0.38 dt (H^9_{syn}), −0.10 dt (H^9_{anti}, ^2J 5.5 Hz). [c] ^1H NMR data: δ1.75 s (2Me), 0.87–1.18 m (4CH), 0.78 dt ($2H^{3,7}_{anti}$, ^2J 3.9, J_{cis} 7.3 Hz), 0.27 q ($2H^{3,7}_{syn}$, $^2J \sim J_{trans}$ 3.9 Hz). [d] ^1H NMR data: δ 3.00 dd (CH_2N, J 5.3 and 7.3 Hz), 1.91 s (Me), 0.86 m (CH), 0.41 m and 0.10 m (CH_2CH_2), 5.9 br s (NH).

in the chosen catalyst. These conditions are found to be optimum for the generation of diazomethane and its methylene transfer to the alkene double bond. Faster addition leads to decomposition of a large quantity of diazomethane into ethylene and cyclopropane which evaporate with nitrogen evolution. Both slower addition and a higher temperature afford partial precipitation of palladium, which may also lead to side-decomposition of diazomethane. Alkanes, CH_2Cl_2, diethyl ether or mixtures of these were found to be superior to other solvents for this process.

The developed procedure was successfully used for cyclopropanation of a wide variety of unsaturated compounds. In general, the competitive cyclopropanation of various double bonds using the *in situ* procedure conforms with the known features of *ex situ* procedures.[1,2] This method appears to be efficient for the preparation of functionalized cyclopropanes. For example, addition of a two-fold excess of *N*-methyl-*N*-nitrosourea to the two-phase system KOH–H_2O/allyl alcohol–Et_2O in the presence of palladium catalysts leads to cyclopropylmethanol in 92% yield. Cyclopropanation of allyl ethers, unsaturated esters and allylamine derivatives also proceeds in good yields (see Table 1).

The following procedure for the preparation of cyclopropane derivatives is representative. The unsaturated compound (0.2 mol), solvent (50–100 ml) and ~80 ml of aqueous KOH solution (40%) are placed in a flask equipped with a stirrer, micropowder addition funnel and a coiled condenser. Then the first portion of *N*-methyl-*N*-nitrosourea (2–3 g) and Pd-based catalyst (0.3 mmol) dissolved in CH_2Cl_2 (5 ml) are added at 10–20 °C. Addition of further portions of solid *N*-methyl-*N*-nitrosourea (~1.5 g min^{-1}, total amount 30–40 g) is carried out after the start of gas evolution. At the end of the reaction the organic layer is separated, the aqueous layer extracted with hexane, the hexane extracts being combined with the original organic layer, and the resulting solution is filtered through Al_2O_3, evaporated and purified by fractional distillation.

In conclusion, we describe an efficient and safe synthesis of various cyclopropanes in high yields by Pd-catalysed cyclopropanation of the corresponding unsaturated compounds with diazomethane generated *in situ*. The new procedure should provide a flexible route for the synthesis of functionalized cyclopropanes, which may be regarded as valuable building blocks in organic synthesis.

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